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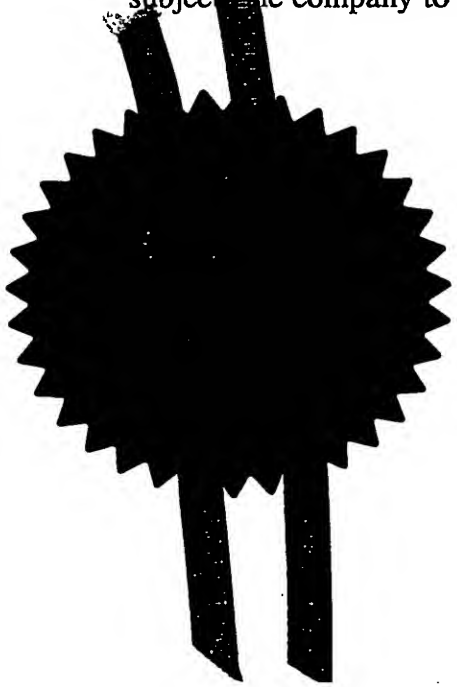

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1. Your reference — LLK/JW/PB60550P

2. Patent application number
(The Patent Office will fill in his part) — 0324574.3 — 21 OCT 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom — 4735870003.

4. Title of the invention — Novel Compositions

5. Name of your agent *(if you have one)*

Corporate Intellectual Property

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GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

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c) any named applicant is a corporate body
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Patents Form 1/77

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Continuation sheets of this form	
Description	11
Claim(s)	2
Abstract	
Drawings	2

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 21-Oct-03

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

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NOVEL COMPOSITIONS

Field of the invention

The present invention relates to an oral dosage form that provides controlled release of an active pharmaceutical agent in different body environments, and to a process for the preparation of such an oral dosage form.

Background to the invention

A controlled release formulation of pharmaceutically active compound, which is designed to release the active compound over the course of several hours and which is administered orally must typically be able to release the active compound in more than one pH environment. For example, after about 2 hours on average the oral dosage form will pass from the patient's stomach at a pH of 1.5 - 2 to the patient's intestines with pH ranging from 5.5 – 7. Since it is unpredictable exactly how long the dosage form will remain in the stomach or the intestines, it is desirable that the release rate is similar under all the pH conditions that will be experienced.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of Example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione. International Patent Application, Publication Number WO 94/05659 discloses certain salts of the compounds of EP 0,306,228. The preferred salt of WO 94/05659 is the maleic acid salt.

The compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione, for convenience referred to below as "Compound A", and its pharmaceutically acceptable salts and solvates have useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Compound A and its pharmaceutically acceptable salts and solvates exhibit a marked pH dependent solubility i.e. more soluble at pH 2 (~15 mg/ml) associated with regions found in the stomach compared to the solubility in the near neutral pHs of the small intestine, pH 7 (~ 0.08 mg/ml). The pH dependent solubility and potential rapid release in the stomach causes difficulties in the formulation or oral dosage forms. It is desirable that release is controlled to take place over a period of hours. Such a formulation would require dosing only once a day, and this is likely to improve patient compliance.

Bodmeier *et al* (Drug Development and Industrial Pharmacy, 1990, 16(9), 15015-1519) have described the use of blends of waxes having different HLB values to control the release of propranolol HCl and theophylline, in a manner that is independent of the pH of the dissolution medium. Such formulations are formed by the heating and subsequent cooling of hard gelatin capsules filled with drug-wax powder blends.

The present invention is based on the finding that certain glyceride based materials can be used as a matrix for oral dosage forms containing Compound A, and the resultant dosage forms have advantageous controlled release properties in the different pH conditions experienced by an oral dosage form after swallowing.

Summary of the invention

In one aspect the present invention provides a sustained release oral dosage form comprising Compound A, or a pharmaceutically acceptable salt or solvate thereof, dispersed in a carrier consisting essentially of a pharmaceutically acceptable waxy mixture of glyceride-based materials having a range of HLB values of 4 to 12 (preferably from 6 to 8), and an average melting point in the range of 50 to 55°C.

For the avoidance of doubt, as used herein the term "HLB value" shall mean hydrophilic-lipophilic balance. HLB values may be measured in accordance with the methods described in A.Gennaro and J. Remington, *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Easton, 1990, 304 and W.C. Griffith, *J. Soc. Cosmetic Chemists*, 1949, 1, 311.

Although the above described waxy materials are a mixture of glycerides and esters that are not expected to cause any toxicological problems, not all the materials falling within the definition have been formally approved for human use. Accordingly it may be necessary to use mixtures of approved materials whose properties approximate to the indicated waxy materials.

Accordingly, in another aspect, the present invention provides a sustained release oral dosage form comprising Compound A, or a pharmaceutically acceptable salt or solvate thereof, dispersed in a carrier consisting essentially of a mixture of

(a) a pharmaceutically acceptable waxy mixture of glyceride-based materials having an HLB value of greater than 12 (preferably greater than 8) and an average melting point in the range of 50 to 55°C, and an amount of

(b) a pharmaceutically acceptable fatty acid glyceride or glyceride mixture having an HLB value less than the HLB value of component (a) and an average melting point in the range of 50 to 55°C,
such that the carrier as a whole has an HLB value of 4 to 12 (preferably between 6 and 8).

Typical oral dosage forms include swallow tablets and capsules.

It is an advantage of the carriers indicated above that they are waxy materials that are molten at elevated temperatures, and can be moulded into tablets containing Compound A, that retain their structural integrity under normal handling conditions without the need for additional tabletting excipients. However it is desirable to apply a conventional soluble film coat on the tablet surface to prevent spoilage when handled by a patient. Also the molten waxy material can be filled into capsule shells, to form swallow capsules containing Compound A.

In all the dosage forms of this invention, the waxy matrix provides advantageous controlled release properties in the different pH conditions to which the matrix is exposed after swallowing. In particular, the release rate of Compound A at acid pHs associated with the stomach pH, is not significantly different from the release rate in the near neutral pH of the small intestine

Brief description of the drawings

Figure 1 is a graph of dissolution against time for two oral dosage forms in accordance with this invention, as disclosed in Examples 1 and 2.
Figure 2 shows dissolution variability observed for cured and uncured oral dosage forms stored at 25°C/60%RH.
Figure 3 shows physical stability observed for cured and uncured oral dosage forms stored at 25°C/60%RH.
Figure 4 shows dissolution rate for the formulation of Example 3.

Detailed description of the invention

The pharmaceutically acceptable waxy mixture of glyceride-based materials is suitably a pharmaceutically acceptable glyceride-based waxy material obtainable by an alcoholysis/esterification reaction between a vegetable oil and a polyethylene glycol.

In the above indicated alcoholysis/esterification reaction, the vegetable oil is preferably a hydrogenated oil so that the fatty acid components are saturated. The reaction between a

hydrogenated vegetable oil and a polyethylene glycol results in a mixture of fatty acid mono-, di-, and tri-glycerides and mono-and di-fatty acid esters of polyethylene glycol.

Most suitably, the vegetable oil is selected so that the predominant fatty acids are palmitic and stearic acids (C16 and C18 acids). A suitable oil is hydrogenated palm oil.

The polyethylene glycol (or PEG) may have a mean molecular weight value ranging from 1300 to 1700. Preferably PEG 1500 is used.

Suitable waxy materials are those indicated as stearoyl macrogol glycerides in the European Pharmacopoeia. Stearoyl macrogolglycerides are mixtures of monoesters, diesters, and triesters of glycerol, and monoesters and diesters of macrogols with a mean molecular mass between 300 and 4000 (nominal value).

As mentioned above, in order to make use of materials already approved as safe for human use, it may be necessary to use a mixture of materials whose properties approximate to a stearoyl macrogol glyceride having a range of HLB values of 4 to 12 (preferably between 6 and 8). For example it may be appropriate to use a stearoyl macrogol glyceride having a higher HLB value and blend it with another glyceride of more hydrophobic character.

A stearoyl macrogol glyceride that is suitable for human use and in which the fatty acid components are predominantly palmitic and stearic acids is available from Gattefosse as Gelucire® 50/13. This is described by the manufacturer as a stearoyl macrogol-32 glyceride which is synthesized by an alcoholysis/esterification reaction using hydrogenated palm oil and PEG 1500 as starting materials. It is therefore a well defined mixture of mono-,di-and triglycerides and mono-and di-fatty acid esters of polyethylene glycol. The predominant fatty acid is palmitostearic acid (C16-C18). It has a melting point in the range 46 – 51°C and an HLB value of 13.

A suitable additional component used in admixture to reduce the average HLB value to the desired range of 4 to 12 (preferably 6 to 8) may be, for example, a fatty acid glyceride mixture, also preferably with palmitic and stearic acids predominating.

A fatty acid glyceride mixture with suitable properties is Gelucire® 50/02 from Gattefosse which has an average melting point of 50°C and an HLB value of 2. Another fatty acid glyceride mixture with suitable properties is Precirol® ATO 5, also from

Gattefosse, which has an average melting point of 55°C and an HLB value of 2. It is synthesized by esterification of glycerol by palmitostearic acid (C16-C18 fatty acid). The raw materials used are of strictly vegetable origin and the reaction process involves no catalyst. The manufacturer indicates that Precirol® ATO 5 is composed of mono-, di and triglycerides of palmitostearic acid, the diester fraction being predominant.

An advantage of the blended carrier is that the proportions of the components can be varied to change the release profile of the carrier i.e. the rate of release can be reduced by increasing the amount of the more hydrophobic component (the component with the lower HLB value). For example, a suitable carrier may be prepared by blending Gelucire® 50/13 and Precirol® ATO 5 in proportions ranging from 40 to 70% of Precirol ATO5.

Also the release rate can be slowed by incorporating a given unit dose in a larger oral dosage form i.e. increasing the weight of carrier relative to a given weight of active compound.

Table 1: Effect of Precirol ATO5 concentration and tablet weight on dissolution profile

Dissolution Timepoint (Hours)	50% Precirol ATO5 – 269 mg tablet weight	60% Precirol ATO5 – 400 mg tablet weight
1	18	15
2	28	24
4	41	36
6	47	39
8	52	42
10	58	44
12	64	47
16	70	54

The above table of data is plotted on Figure 1.

Swallow tablets of this invention are conveniently prepared by melting the waxy material, or melt-blending two materials when used, and dispersing Compound A or its salt or solvate in the molten wax. The molten blend is then filled in to moulds and allowed to solidify. The tablets thus formed are preferably provided with a film coat. Suitable

coating agents include hydroxypropyl methylcellulose aqueous dispersions (which may include lactose or polydextrose), or preferably polyvinyl alcohol aqueous dispersions.

Swallow capsules of this invention are conveniently prepared by melting the waxy material, or melt-blending two materials when used, and dispersing Compound A or its salt or solvate in the molten wax. The molten blend is then filled in to capsule shells, such as hard gelatin capsule shells, in conventional manner.

Certain macrogol glycerides exist in more than one polymorphic form. We have found that is advantageous to heat treat the oral dosage forms after moulding and coating tablets, or filling capsules, by heating at a temperature below the melting point of the carrier, to convert the macrogol glyceride to its most stable form. Surprisingly this also results in a significant reduction in variability of the dissolution profile between individual oral dosage forms, which is a great advantage in accurate dosing. Heat treatment preferably takes place at 40°C, for between 16 and 72 hours.

Table 2: Dissolution variability between cured and uncured oral dosage forms stored at 25°C/60%RH.

Dissolution Timepoint (Hours)	Initial immediately after Curing	3 Months Curing at 40°C for 48 hours	3 Months No Curing
	Max-Min Range between n=6 dosage forms (% dissolved)		
8	13	3	20
12	14	2	32
16	14	2	48

Figure 2 and Figure 3 show dissolution variability and physical stability observed for cured and uncured oral dosage forms stored at 25°C/60%RH.

Accordingly in a further aspect, the present invention provides a method of preparing a sustained release oral dosage, which comprises dispersing Compound A, or a pharmaceutically acceptable salt or solvate thereof, in a molten carrier consisting essentially of a pharmaceutically acceptable waxy mixture of glyceride-based materials, having an HLB value of 4 to 12, and an average melting point in the range of 50 to 55°C, filling the molten mixture into tablet moulds or capsule shells, allowing the carrier to solidify, and maintaining the solidified dosage form at a temperature of at least 40°C, but

below the melting point of the carrier, for a time sufficient to allow the carrier to achieve a stable polymorphic form.

The invention also provides a method of preparing a sustained release oral dosage form, which comprises dispersing Compound A, or a pharmaceutically acceptable salt or solvate thereof, in a molten carrier consisting essentially of a mixture of
(a) a pharmaceutically acceptable waxy mixture of glyceride-based materials having an HLB value of greater than 12 and an average melting point in the range of 50 to 55°C, and an amount of
(b) a pharmaceutically acceptable fatty acid glyceride or glyceride mixture having an HLB value less than the HLB value of component (a) and an average melting point in the range of 50 to 55°C,
such that the carrier as a whole has an HLB value of 4 to 12,
filling the molten mixture into tablet moulds or capsule shells, allowing the carrier to solidify, and maintaining the solidified dosage form at a temperature of at least 40°C, but below the melting point of the carrier, for a time sufficient to allow the carrier to achieve a stable polymorphic form.

The compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione, Compound A, and its pharmaceutically acceptable salts and solvates have useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof; 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes. Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially Atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type

II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

The compositions of the present invention are also indicated to be useful in the treatment and/or prohylaxis of certain other conditions in which agonism of the PPAR-γ receptor pathway is beneficial.

The compositions of the invention are indicated to be useful in the treatment of osteoporosis, psoriasis and Alzheimer's Disease.

The present invention provides a method of treating the above disorders by administering an effective amount of the sustained release oral dosage forms of the invention to a sufferer in need thereof.

The present invention further provides the use of Compound A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable glyceride-based waxy mixture of materials in the manufacture of a sustained release oral dosage form for treating the above disorders.

In the treatment and/or prophylaxis of the above-mentioned conditions, the oral dosage forms of this invention may be taken in amounts so as to provide Compound A in suitable doses, such as those disclosed in EP 0,306,228, WO 94/05659 or WO 98/55122.

In one particular aspect, the oral dosage form comprises 2 to 12 mg of Compound A.

Suitably the oral dosage form comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound A.

Particularly, the oral dosage form comprises 2 to 4, 4 to 8 or 8 to 12 mg of Compound A.

Particularly, the oral dosage form comprises 2 to 4 mg of Compound A.

Particularly, the oral dosage form comprises 4 to 8 mg of Compound A.

Particularly, the oral dosage form comprises 8 to 12 mg of Compound A.

Preferably, the oral dosage form comprises 2 mg of Compound A.

Preferably, the oral dosage form comprises 4 mg of Compound A.

Preferably, the oral dosage form comprises 8 mg of Compound A.

Most preferably the oral dosage forms are formulated to deliver a dose of 8 mg of Compound A (as the free base) in a sustained release as a once a day dose.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts, of Compound A in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of Compound (I) *per se*. For example, 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt, which contains 2 mg of Compound (I).

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

No adverse toxicological effects are indicated in the above mentioned treatments for the oral dosage forms of the invention.

The invention is illustrated by the following Examples.

Example 1

Gelucire 50/13 (Gattefosse) and Precirol ATO5 (Gattefosse) were melt blended at 70 °C. The temperature of the blend was allowed to decrease to between 52 and 57°C. Compound (A) as the maleate (GlaxoSmithKline) was added to the molten blend, so that the resultant mixture contained the three components in the proportions

	% w/w
Compound (A) Maleate	4
Gelucire 50/13 (wax)	46
Precirol ATO5 (wax)	50

The molten mixture was filled into rubber tablet moulds and allowed to cool, to give tablets of total weight 269 mg, each containing 8 mg of Compound (A) (measured as the free base). Tablets were coated with a solution of Opadry 2, to a 6 % weight gain.

The moulded and coated tablets were then heated for 48 hours at 40°C, to improve the physical stability, and the reproducibility of dissolution release rates.

Example 2

Gelucire 50/13 (Gattefosse) and Precirol ATO5 (Gattefosse) were melt blended at 70 °C. The temperature of the blend was allowed to decrease to between 52 and 57°C. Compound (A) Maleate (GlaxoSmithKline) was added to the molten blend, so that the resultant mixture contained the three components in the proportions

	% w/w
Compound (A) Maleate	2.65
Gelucire 50/13 (wax)	37.35
Precirol ATO5 (wax)	60

The molten mixture was filled into rubber tablet moulds and allowed to cool, to give tablets of total weight 400 mg, each containing 8 mg of Compound (A) (measured as the free base). Tablets were coated with a solution of Opadry 2, to a 6 % weight gain.

The moulded and coated tablets were then heated for 48 hours at 40°C, to improve the physical stability, and the reproducibility of dissolution release rates.

Example 3

Gelucire 50/13 (Gattefosse) and Precirol ATO5 (Gattefosse) were melt blended at 70 °C. The temperature of the blend was allowed to decrease to between 55 and 60°C. Compound (A) Maleate (GlaxoSmithKline) was added to the molten blend, so that the resultant mixture contained the three components in the proportions

	% w/w
Compound (A) Maleate	4
Gelucire 50/13 (wax)	46
Precirol ATO5 (wax)	50

The molten mixture was filled into capsules and allowed to cool. Each capsule contained 8 mg of rosiglitazone (measured as the free base).

Dissolution Tests

Dissolution rates for the formulations of Examples 1 and 2 were measured starting at pH 1.5 with an adjustment to pH 6.8 after 4 hours, as an assumed time for residence in the fed stomach before emptying into the intestines. The medium for this dissolution test is initially an aqueous solution of sodium chloride and hydrochloric acid, pH 1.5 to mimic the pH found in the stomach environment. This medium is then titrated to pH 6.8 by the addition of aqueous sodium dodecyl sulfate and an aqueous solution of sodium acetate and tris(hydroxymethyl)methylamine after 4 hours to mimic the pH found in the intestine. The results are plotted in Figure 1. The formulation of Example 2 gave a slower release of rosiglitazone than the tablet of Example 1, by virtue of the increased amount of Precirol ATO 5, giving a more hydrophobic character to the matrix, and because of the increased tablet size.

Dissolution rates for the formulation of Example 3 were measured starting at pH 1.5 with an adjustment to pH 7.4 after 2 hours, as an assumed time for residence in the fasted stomach before emptying into the intestines. The medium for this dissolution test is initially an aqueous solution of sodium chloride and hydrochloric acid, pH 1.5 to mimic the pH found in the stomach environment. This medium is then titrated to pH 7.4 by the addition of aqueous sodium dodecyl sulfate and an aqueous solution of sodium acetate and tris(hydroxymethyl)methylamine after 2 hours to mimic the pH found in the intestine. The results are shown in Figure 4.

CLAIMS

1. A sustained release oral dosage form comprising Compound A, or a pharmaceutically acceptable salt or solvate thereof, dispersed in a carrier consisting essentially of pharmaceutically acceptable waxy mixture of glyceride-based materials, having an HLB value of 4 to 12, and an average melting point in the range of 50 to 55°C.

2. A sustained release oral dosage form comprising Compound A, or a pharmaceutically acceptable salt or solvate thereof, dispersed in a carrier consisting essentially of a mixture of
(a) a pharmaceutically acceptable waxy mixture of glyceride-based materials having an HLB value of greater than 12 and an average melting point in the range of 50 to 55°C, and an amount of
(b) a pharmaceutically acceptable fatty acid glyceride or glyceride mixture having an HLB value less than the HLB value of component (a) and an average melting point in the range of 50 to 55°C,
such that the carrier as a whole has an HLB value of 4 to 12.

3. An oral dosage form according to any of claims 1 to 2 in which the pharmaceutically acceptable waxy mixture of glyceride-based materials is waxy material obtainable by an alcoholysis/esterification reaction between a vegetable oil and a polyethylene glycol.

4. An oral dosage form according to claim 3 in which the vegetable oil is a hydrogenated oil.

5. An oral dosage form according to claim 4 in which the vegetable oil is hydrogenated palm oil.

6. An oral dosage form according to any one of claims 1 to 4 in which the fatty acids of the glyceride are predominantly palmitic and stearic acids.

7. An oral dosage form according to any one of claims 1 to 6, in which the carrier and compound A are moulded to form a tablet.

8. An oral dosage form according to any one of claims 1 to 6, in which the carrier and compound A are filled into capsule shells to form swallow capsules.

9. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, which comprises administering an effective amount of a sustained release oral dosage form as claimed in any one of claims 1 to 8 to a sufferer in need thereof.

10. Use of Compound A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable waxy mixture of glyceride-based materials in the manufacture of a sustained oral dosage form for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

11. A method of preparing a sustained release oral dosage form; which comprises dispersing Compound A, or a pharmaceutically acceptable salt or solvate thereof, in a molten carrier consisting essentially of a pharmaceutically acceptable waxy mixture of glyceride-based materials, having an HLB value of 4 to 12, and an average melting point in the range of 50 to 55°C, filling the molten mixture into tablet moulds or capsule shells, allowing the carrier to solidify, and maintaining the solidified dosage form at a temperature of at least 40°C, but below the melting point of the carrier, for a time sufficient to allow the carrier to achieve a stable polymorphic form.

12. A method of preparing a sustained release oral dosage form; which comprises dispersing Compound A, or a pharmaceutically acceptable salt or solvate thereof, in a molten carrier consisting essentially of a mixture of

(a) a pharmaceutically acceptable waxy mixture of glyceride-based materials having an HLB value of greater than 12 and an average melting point in the range of 50 to 55°C, and an amount of

(b) a pharmaceutically acceptable fatty acid glyceride or glyceride mixture having an HLB value less than the HLB value of component (a) and an average melting point in the range of 50 to 55°C,

such that the carrier as a whole has an HLB value of 4 to 12,

filling the molten mixture into tablet moulds or capsule shells, allowing the carrier to solidify, and maintaining the solidified dosage form at a temperature of at least 40°C, but below the melting point of the carrier, for a time sufficient to allow the carrier to achieve a stable polymorphic form.

Figure 1

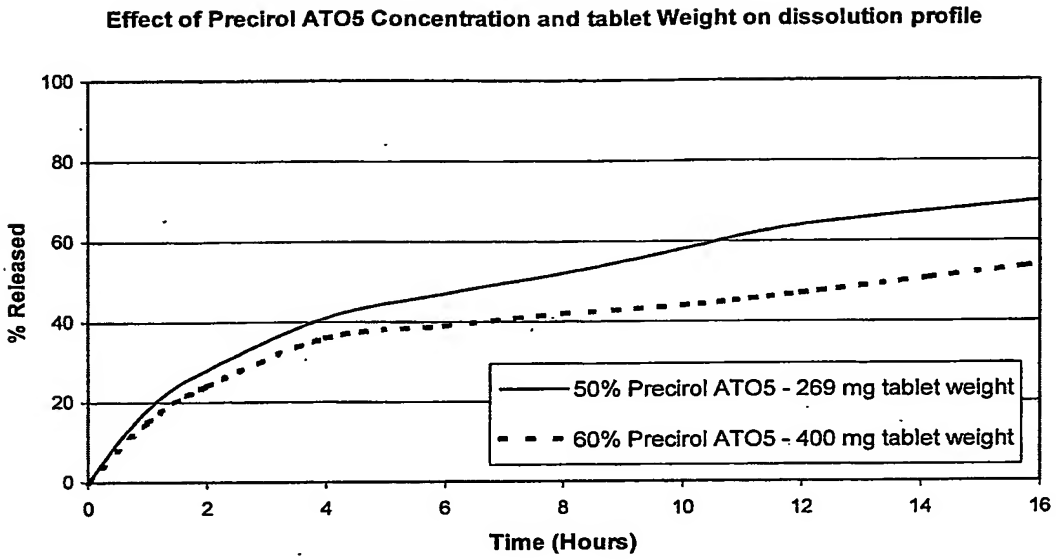

Figure 2

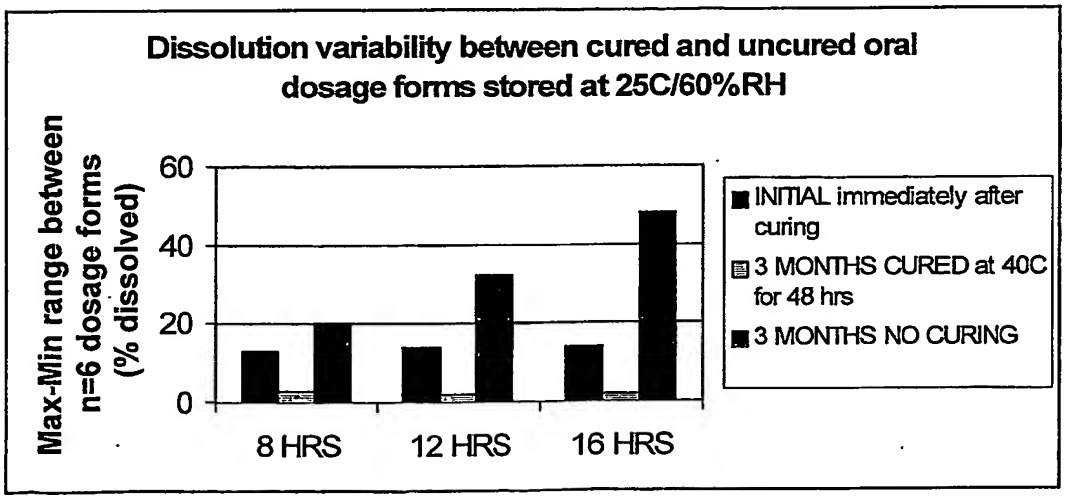

Figure 3

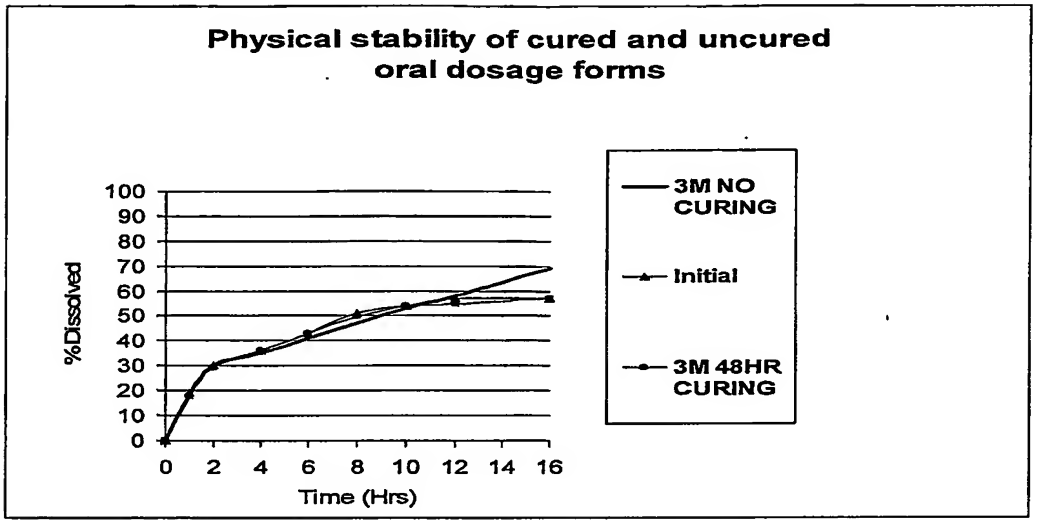

Figure 4